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| EXAMINER | |
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| ART UNIT | PAPER NUMBER |
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| 1652 | |

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Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/089,147 | KINDL ET AL. | |
| | Examiner | Art Unit | |
| | Yong D. Pak | 1652 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *22 May 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *5,7 and 15-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6 and 8-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

This application is a 371 of PCT/EP00/09912.

The amendment filed on May 22, 2006, amending claims 1-4 and 10, has been entered.

Claims 1-20 are pending. Claims 5, 7 and 15-20 are withdrawn. Claims 1-4, 6 and 8-14 are under consideration.

### *Response to Arguments*

Applicant's amendment and arguments filed on May 22, 2006, have been fully considered and are deemed to be persuasive to overcome the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

### *Claim Objections*

Claim 4 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 4 is drawn to a polynucleotide encoding a fusion protein comprising a polypeptide have at least 80% homology to SEQ ID NO:2. However, claim 1, from which claim 4 depends from, is drawn to a polynucleotide encoding a fusion protein comprising a polypeptide have at least 95% homology to SEQ ID NO:2. Appropriate correction is required.

Claim 1 is objected to because of the following informalities: a conjunction is missing between clauses b) and c). Appropriate correction is required.

Claims 2-4, 9 and 11-14 are objected to because of the following informalities: claims 2-4 should recite "The isolated nucleic acid sequence as claimed in claim 1", claim 9 should recite "The vector as claimed in claim 8" and claims 11-14 should recite "The non-human organism as claimed in claim 10", since these claims are all depended claims . Appropriate correction is required.

Claims 6 and 8 are objected to because of the following informalities: claims 6 and 8 should recite "the nucleic acid sequence as claimed in claim 1", since the sequences refer back to a sequence in claim 1. Appropriate correction is required.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> **The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.**

Claims 1 and 4 and claims 2-3, 6 and 8-14 depending therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 4 recite the phrase "depicted in". The metes and bounds of the phrase in the context of the claims are not clear. It is not clear to the Examiner if the

recited nucleic acid sequence has the nucleotide sequence of SEQ ID NO:1 or if the recited polypeptide has the amino acid sequence of SEQ ID NO:2 or whether the sequences are representative members of a genus. Examiner suggests amending the phrase as, for example, "the polypeptide comprising the amino acid sequence of SEQ ID NO:2" or "the nucleic acid sequence comprising the nucleotide sequence of SEQ ID NO:1".

In response to the previous Office Action, applicants have traversed the above rejection.

Applicants argue that the language of the claims should be read in light of the specification. However, the specification does not provide a definition for the phrase "depicted in SEQ ID NO:1" or "depicted in SEQ ID NO:2". Therefore, it is not clear to the Examiner if the recited nucleic acid sequence has the nucleotide sequence of SEQ ID NO:1 or if the recited polypeptide has the amino acid sequence of SEQ ID NO:2 or whether the sequences are representative members of a genus.

Hence the rejection is maintained.

Claims 2 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2 recites the phrase "wherein a nucleic acid sequence is used as a part of the fusion protein encoding a protein selected from the protein groups of the fatty acid desaturase(s)". The metes and bounds of the above phrase in the context of the claim

are not clear. The phrase recites "protein selected from the protein groups", but only one protein group is recited. Therefore, it is not clear to the Examiner what protein groups are encompassed by the above phrase. Examiner requests clarification of the above phrase.

Claims 2-3 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 2-3 recite the phrases "wherein a nucleic acid sequence is used as a part of the fusion protein encoding a protein selected from the protein groups of the fatty acid desaturase(s)" and "wherein a nucleic acid sequence is used as a part of the fusion protein encoding a: Δ-4 desaturase". It is not clear to the Examiner how a "fusion protein" encodes another protein. It is also not clear how nucleic acid sequences are used as part of a protein. The phrases are highly confusing and does not make any scientific sense. Examiner requests clarification of the above phrase.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 6 and 8-14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject

matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claims 1-3, 6 and 8-14 are drawn to a polynucleotide encoding a fusion protein comprising a polypeptide having at least 95% homology to SEQ ID NO:2, and vectors and host cells comprising said polynucleotide. However, the polynucleotide encoding a fusion protein comprising a polypeptide having at least 95% homology to SEQ ID NO:2 was not described in the application as originally filed nor in any of its parent applications. The specification as filed contains disclosure of only polynucleotides encoding a fusion protein comprising a polypeptide having at least 50, 60, 70 or 80% homology to SEQ ID NO:2. Therefore, claims 73-82 contain new matter.

Given this lack of description of the polynucleotide encoding a fusion protein comprising a polypeptide having at least 95% homology to SEQ ID NO:2 and vectors and host cells comprising said polynucleotide in the claims, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the inventions of claims 1-3, 6 and 8-14 at the time of filing of the instant application.

Claims 1-4, 6 and 8-14 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-4, 6 and 8-14 are drawn to a polynucleotide encoding a fusion protein comprising a polypeptide having at least 80% or 95% sequence identity to SEQ ID NO:2 and Δ-4 desaturase. The claims encompass polynucleotides encoding a fusion protein comprising polypeptides having at least 80% or 95% sequence identity to SEQ ID NO:2 and Δ-4 desaturase, wherein said polypeptide has any activity or no activity and the resulting fusion protein has any activity or no activity. Therefore, these claims are drawn to a genus polynucleotides encoding a fusion protein comprising Δ-4 desaturase and a polypeptide having 80% or 95% amino acid sequence identity with SEQ ID NO:2, wherein said fusion protein has any function or no function. There is no disclosure of any particular structure to function/activity relationship in the disclosed species.

The claims are drawn to many functionally unrelated polynucleotides are encompassed within the scope of these clams, including partial sequences. The genus of these polynucleotides comprise a large variable genus with the potentiality of encompassing many different polynucleotides encoding fusion proteins having different activity or no activity. The specification discloses only a single species of the claimed genus, a polynucleotide encoding a fusion protein comprising a polypeptide of SEQ ID NO:2 and a Δ-4 desaturase, wherein said desaturase continues to have Δ-4 desaturase activity and SEQ ID NO:2 targets said desaturase to lipid bodies. The specification fails to describe additional representative species of the polynucleotides by any identifying characteristics or properties of the encoded polypeptides, for which no predictability of function is apparent. Therefore, one skilled in the art cannot reasonably conclude that

the applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

In response to the previous Office Action, applicants have traversed the above rejection. Applicants argue that since applicants have amended the claims to recite "95%", the claims meet the written description requirement. Examiner respectfully disagrees. Claim 4 remains to be drawn to polynucleotides having 80% sequence identity to SEQ ID NO:2, wherein said polynucleotide encodes a fusion proteins having any or no or unknown activity. Further, the claims remain drawn to a genus of polynucleotides encoding a fusion protein comprising Δ-4 desaturase and a polypeptide having 80% or 95% amino acid sequence identity with SEQ ID NO:2, wherein said polypeptide has any activity or no activity and the resulting fusion protein has any activity or no activity. As discussed in the written description guidelines, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, **by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.** A representative number of

species means that the species which are adequately described are representative of the entire genus. **Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.** Satisfactory disclosure of a representative number depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. For inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus. In the instant case the claimed genus of the claims includes species which are widely variant in function. The genus of the claims is functionally diverse as it encompasses polynucleotides encoding polypeptides with LBLOX activity, polypeptides that target proteins to lipid bodies and those which lack such activity and those with no activity. As such, the description of solely structural features present in all members of the genus is not sufficient to be representative of the attributes and features of the entire genus.

Hence the rejection is maintained.

Claims 1-4, 6 and 8-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a polynucleotide encoding a fusion protein comprising a polypeptide of SEQ ID NO:2 and a Δ-4 desaturase, wherein said desaturase continues to have Δ-4 desaturase activity and SEQ ID NO:2 targets said desaturase to lipid bodies, does not reasonably provide enablement for a polynucleotide

comprising any polynucleotides encoding any Δ-4 desaturase and a variant or mutant of SEQ ID NO:1 encoding a polypeptide having at least 80 or 95% amino acid sequence identity to SEQ ID NO:2, vectors and transformed host cells comprising the above, wherein the encoded polypeptide of SEQ ID NO:2 has any function or no function at all and wherein the final activity of fusion protein is unknown. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Claims 1-4, 6 and 8-14 are directed to a fusion polynucleotide comprising a polynucleotide encoding an enzyme involved in fatty acid/lipid metabolism and a variant, mutant or recombinant of SEQ DI NO:1 encoding a polypeptide having at least 80-95% amino acid sequence identity to SEQ ID NO:2, vectors comprising said polynucleotide and organisms comprising said polynucleotide. Therefore, these claims are drawn to polynucleotides having any structure.

The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polynucleotides comprising,

variants and mutants broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to a polynucleotide encoding a fusion protein comprising a specific fatty acid/lipid metabolism enzymes such as Δ-4 desaturase and the SEQ ID NO:2.

It would require undue experimentation of the skilled artisan to make and use the claimed polynucleotides. The specification provides no guidance with regard to the making of variants and mutants of SEQ ID NO:2 or with regard to other uses. In view of the great breadth of the claim, amount of experimentation required to make the claimed polynucleotides, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary structure, the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the polynucleotides encompassed by the claims.

While enzyme isolation techniques, recombinant and mutagenesis techniques are known, and it is routine in the art to screen for multiple substitutions or multiple modifications as encompassed by the instant claims, the specific amino acid positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in

any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of polynucleotides of SEQ ID NO:1 encoding a polypeptide having at least 80 or 95% amino acid sequence identity to SEQ ID NO:2 because the specification does not establish: (A) regions of the encoded protein structure which may be modified without affecting LBLOX activity or its ability to target foreign proteins to lipid bodies; (B) the general tolerance of LBLOX to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue with an expectation of obtaining the desired biological function; (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful; (E) the specification is also silent regarding the final activity of fusion proteins of SEQ ID NO:2.

The claims also broadly encompass not only polynucleotides encoding LBLOX or fragments of LBLOX having ability to target foreign proteins to lipid bodies and enzymes of fatty acid/lipid metabolism, but polynucleotides encoding polypeptides having any function or having no function. Therefore, the breadth of these claims is much larger than the scope enabled by the specification.

The specification does not teach how to make variants of polynucleotides of SEQ ID NO:1 or polynucleotides of fatty acid/lipid metabolism encoding polypeptides having any function. The function of a polypeptide cannot be predicted from its structure and

the specification does not teach how to use polypeptides having any function or having no activity. The quantity of experimentation in this area is extremely large since there is significant variability in the activity of the polynucleotides in the claims. It would require significant study to identify the actual function of the encoded polypeptides and identifying a use for the encoded polypeptide would be an inventive, unpredictable and difficult undertaking. This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

The art is extremely unpredictable with regard to protein function in the absence of realizable information regarding its activity. Even very similar proteins may have every different functions. In the current case, where no specific information is known regarding the function, it is entirely unpredictable what function and activity will be found for the protein. The prior art does not resolve this ambiguity, since no prior art activity is identified for the encoded polypeptides.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including polynucleotide comprising variants and mutants of any polynucleotides of fatty acid/lipid metabolism and any mutants and variants of SEQ ID NO:1 encoding polypeptides having any structure and any function. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of variants or mutants of SEQ ID NO:1 and polynucleotides of fatty

acid/lipid metabolism having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

In response to the previous Office Action, applicants have traversed the above rejection. Applicants argue that one of ordinary skill in the art would be able to create the working examples and the guidance in making such examples are minimal and routine. Examiner respectfully disagrees. The specification discloses only the a polynucleotide encoding a fusion protein comprising a specific fatty acid/lipid metabolism enzymes such as Δ-4 desaturase and the SEQ ID NO:2, wherein the LBLOX of SEQ ID NO:2 targets Δ-4 desaturase to lipid bodies. However, the speciation fails to provide any information as to (1) specific substrates associated with polynucleotides encoding SEQ ID NO:2 and its variants, (2) structural elements required in a polypeptide in targeting foreign polypeptides to lipid bodies, or (3) which are the structural elements in the polypeptide of SEQ ID NO:2 that are essential in targeting foreign polypeptides to lipid bodies. No correlation between structure and function of polypeptides that target foreign polypeptides to lipid bodies has been presented. There is no information or guidance as to which amino acid residues in the polypeptides encoded by SEQ ID NO:2 can be modified and which ones are to be conserved to create a polypeptide displaying the same activity as that of the polypeptides of SEQ ID NO:2 in a fusion polypeptide. Without specific guidance, those skilled in the art will be

subjected to undue experimentation of making and testing each of the enormously large number of mutants that results from such experimentation.

Applicants also argue that there is no undue experimentation and the presence of inoperative embodiment within the scope of a claim does not necessarily render a claim non-enabled. Examiner respectfully disagrees. There is no information or guidance as to which amino acid residues in the polypeptides encoded by SEQ ID NO:2 can be modified and which ones are to be conserved to create a polypeptide displaying the same activity as that of the polypeptides of SEQ ID NO:2 in a fusion polypeptide. Without specific guidance, those skilled in the art will be subjected to undue experimentation of making and testing each of the enormously large number of mutants that results from such experimentation. Since the scope of the claims require an undue experimentation to make and use the claimed polynucleotides, the claims are also not commensurate with the enablement provided by the disclosure with regard to inoperative embodiments encompassed by the claims. Although the presence of inoperative embodiments within the scope of the claims does not necessarily render a claim non-enabled, the standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art. *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984). The scope of the claims are not enabled when undue experimentation is involved in determining those embodiments that are operable. In the instant case, the claims read on significant numbers of inoperative embodiments, rendering the claims

non-enabled, since the specification does not clearly identify the operative embodiments and undue experimentation is involved in determining those that are operative. *Atlas Powder Co. v. E.I. duPont de Nemours & Co.*, 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984); *In re Cook*, 439 F.2d 730, 735, 169 USPQ 298, 302 (CCPA 1971).

Applicants also argue that since computational techniques were available to arrive at the claimed sequences, one of ordinary skill in the art would have ready knowledge of and predictability of activity after amino acid substitutions. Examiner respectfully disagrees. First, the claims are drawn to polynucleotides encoding polypeptide having unknown activity or no activity. The art is extremely unpredictable with regard to protein function in the absence of realizable information regarding its activity. Even very similar proteins may have every different functions. In the current case, where no specific information is known regarding the function, it is entirely unpredictable what function and activity will be found for the protein. The prior art does not resolve this ambiguity, since no prior art activity is identified for the encoded polypeptides. Second, while a skilled artisan can produce variants of the polypeptide of SEQ ID NO: 2 having the recited structural characteristics using well-known and widely used techniques in the art, the amount of experimentation required is not routine nor predictable to the fact that the claims encompass an extremely large number of polynucleotides comprising, variants and mutants broadly encompassed by the claims. Guo et al.(PNAS 101(25):9205-9210, 2004 –form PTO-892) teaches that the percentage of random single substitution mutations which inactivate a protein for the protein 3-methyladenine DNA glycosylase is 34% (*x* factor) and that this number

appears to be consistent with other studies in other proteins as well (Abstract). Guo et al. further shows in Table 1 that the percentage of active mutants for multiple mutants appears to be exponentially related to this by the simple formula $(.66)^x$ x 100% where x is the number of mutations introduced and 0.66 is the probability of a protein to remain active after one amino acid change (0.66= 1-0.34). If one were to apply this estimate to the instant 80 or 95% sequence identity to SEQ ID NO: 2 (244 amino acids; 12 mismatches = 0.05 x 244 for 95% or 49 mismatches = 0.20 x 244 for 80%), only $(.66)^{12}$ x 100% or .68% of random mutants having 95% sequence identity to SEQ ID NO: 2 would be active or $(.66)^{49}$ x 100% or 1.44X $10^{-7}$% of random mutants having 80% sequence identity to SEQ ID NO: 2 would be active. As indicated above, 80 or 95% sequence identity to SEQ ID NO: 2 allows for 12 or 49 amino acid changes. Therefore, to find a single active mutant within random mutants having 80 or 95% sequence identity to SEQ ID NO: 2, one of skill in the art would have to screen over several 147 to 700 million mutants (100/1.05 x $10^{-7}$%).

Hence the rejection is maintained.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-4, 6 and 8-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hohne et al., Ohlrogge et al. and Yamamoto et al.

Claims 1-4, 6 and 8-14 are drawn to a polynucleotide encoding a fusion protein comprising a Δ-4 desaturase and SEQ ID NO:2, vector comprising said polynucleotide and *S. cerevisiae* comprising said polynucleotide.

Hohne et al. (form PTO-1449 – Eur. J. Biochem. 241, 1996: 6-11 and form PTO-892 - NCBI Accession CAA63483.1) discloses a polynucleotide encoding a lipid body lipoxygenase (LBLOX), wherein amino acid at positions 1-244 is 100% identical to SEQ ID NO:2 (page 2, 3rd paragraph and see Sequence Alignment – cited previously on form PTO-892). Hohne et al. teaches that LBLOX is synthesized and transported to lipid bodies at the beginning of lipid body mobilization, during which fatty acids/lipids are metabolized (pages 6 and 8-9). Hohne et al. also teaches that the N-terminal region of LBLOX may represent a targeting sequence and may be responsible for the attachment of LBLOX to the lipid body surface (page 10). Hohne et al. also teaches that a

comparison between the molecular mass of the *in vitro* and *in vivo* form of LBLOX did not indicate significant proteolytic processing and LBLOX is only slightly higher in mass than its cytosolic form, suggesting that the N-terminal region of LBLOX contains a recognition site for lipid bodies (page 10). It is well within the skill available in the art to identify sequences in the N-terminal region of LBLOX that target LBLOX to lipid bodies and attach any protein to such sequences, in order to target the protein of interest to lipid bodies. Further, the claims do not recite that the fusion partner to the desaturase consist of SEQ ID NO:2, therefore, full length LBLOX of Hohne et al. or its N-terminal region comprising SEQ ID NO:2, are encompassed by scope of the claims.

The difference between the reference of Hohne et al. and the instant claims is that the reference of Hohne et al. does not teach a polynucleotide encoding a fusion protein comprising a Δ-4 desaturase fused to LBLOX, vectors comprising said polynucleotide or microorganism comprising said polynucleotide.

Ohlrogge et al. (form PTO-892 - Oils-Fats-Lipids 1995) teaches a polynucleotide encoding a Δ-4 desaturase, which is an enzyme of fatty acid/lipid metabolism (abstract).

Yamamoto et al. (form PTO-892 – U.S. Patent No. 5,506,120) teaches a polynucleotide encoding a fusion protein, linking proteins via a regulatory signal, vectors comprising said polynucleotide and a *Saccharomyces cerevisiae* comprising said polynucleotide (abstract and Columns 5-14).

Therefore, combining the teachings of the above references, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was

made to make a polynucleotide encoding a fusion protein comprising the full length LBLOX of Hohne et al. and a target protein of interest, such as enzymes involved in fatty acid/lipid metabolism. Alternatively, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was to identify sequences that target LBOX to lipid bodies in order to target other proteins of interest, such as enzymes involved in fatty acid/lipid metabolism, to lipid bodies. Upon identifying the targeting sequences, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to make a polynucleotide encoding a fusion protein comprising said sequences and a fatty acid/lipid metabolism enzyme of interest, such as the desaturase of Ohlrogge et al., using the method taught by Yamamoto et al. One having ordinary skill in the art would have been motivated to use full length LBLOX or to identify sequences that target LBLOX to lipid bodies, in order to use them to target other proteins, such as enzymes involved in fatty acid/lipid metabolism, to lipid bodies, and make a polynucleotide encoding a fusion comprising said sequence and desaturase, thereby directing the enzyme to the site where its activity is desired. One of ordinary skill in the art would have had a reasonable expectation of success in making the polynucleotide since making polynucleotides encoding fusion proteins is well known in the art, as taught by Yamamoto et al. One of ordinary skill in the art would have had a reasonable expectation of success in making a fusion protein comprising the full length LBLOX to target protein to lipid bodies since Hohne et al. teaches that the full length LBLOX is targeted to lipid bodies. Similarly, one of ordinary skill in the art would have had a reasonable expectation of success in identifying N-terminal sequences of LBLOX

of Hohne et al. that target proteins to lipid bodies and making a fusion protein comprising such N-terminal sequences to target protein to lipid bodies since Hohne et al. teaches that the N-terminal region of the LBLOX may be responsible for targeting proteins to lipid bodies.

Therefore, Hohne et al., Ohlrogge et al. and Yamamoto et al. in combination render claims 1-4, 6, 8-9 and 10-14 *prima facie* obvious to those skilled in the art.

In response to the previous Office Action, applicants have traversed the above rejection.

Applicants argue that Examiner has inappropriately bypassed analysis of a number of Applicants' prior arguments by stating that said arguments attached the reference individually. It is not clear to which arguments and its corresponding reply by Examiner applicants are referring to. Also, all arguments presented by applicants were responded.

Applicants argue that Hohne et al. fails to teach or suggest the targeting of fusion proteins to liposomes, fails to teach anything in the technical field of fusion proteins; the reference is related to the physiological characterization of a lipoxygenase from cucumber, and therefore, one of ordinary skill in the art would not be motivated to combine or modify said cited art. Examiner respectfully disagrees. The rejection is an obviousness rejection, not an anticipation rejection. Therefore, Hohne et al. does not have to teach all limitations of the claimed invention. What Hohne et al. discloses is that the N-terminal portion of CSLBLOX is the targeting sequence toward lipid bodies. With this teaching at hand, one having ordinary skill in the art would have been motivated to

use it as a targeting sequence. The teachings of fusion proteins is provided by Yamamoto et al.

Applicants also argue that Ohlrogge et al. discloses only a polynucleotide encoding a desaturase and its function in fatty acid biosynthesis and fails to teach or suggest about targeting sequences or fusion proteins. Again, the rejection is an obviousness rejection, not an anticipation rejection. Therefore, Ohlrogge et al. does not have to teach targeting sequences or fusion proteins. The reference of Ohlrogge et al. is relied upon for its teaching of polynucleotide encoding a Δ-4 desaturase, which is an enzyme of fatty acid/lipid metabolism (abstract). Upon combining the teachings of the above references, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to make a polynucleotide encoding a fusion protein comprising the LBLOX of Hohne et al. and the desaturase of Ohlorogge et al., in order to target other proteins of interest, such as enzymes involved in fatty acid/lipid metabolism such as a desaturase, to lipid bodies.

Applicants also argue that Yamamoto et al. fails to teach or suggest the fusion process for combining LBLOX and desaturase. Again, the rejection is an obviousness rejection, not an anticipation rejection. Therefore, Yamamoto et al. does not have to teach a process for combining LBLOX and desaturase. Further, the claims are drawn to a polynucleotide and not a method of targeting proteins, and the claims do not recite targeting proteins to liposomes or lipid bodies. Also, the reference of Yamamoto et al. is relied upon for its teaching of teaches a polynucleotide encoding a fusion protein, linking proteins via a regulatory signal, vectors comprising said polynucleotide and a

*Saccharomyces cerevisiae* comprising said polynucleotide (abstract and Columns 5-14). Upon Combining the teachings of the above references, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was length made to make a polynucleotide encoding a fusion protein comprising the LBLOX of Hohne et al. and a target protein of interest, such as enzymes involved in fatty acid/lipid metabolism.

Applicants also argue that there is no motivation to combine the references, without offering any arguments as to why there is not motivation to combine the references. As discussed in the rejection, one having ordinary skill in the art would have been motivated to use full length LBLOX or to identify sequences that target LBLOX to lipid bodies, in order to use them to target other proteins, such as enzymes involved in fatty acid/lipid metabolism, to lipid bodies, and make a polynucleotide encoding a fusion comprising said sequence and desaturase, thereby directing the enzyme to the site where its activity is desired

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In the instant case, it should be noted that Hohne et al. teaches that the N-

terminal region of the LBLOX targets proteins to lipid bodies and that the knowledge of identifying sequences in the N-terminal region of LBLOX that target LBLOX to lipid bodies and attach any protein to such sequences, in order to target the protein of interest to lipid bodies, was well known and within the level of one having ordinary skill in the art at the time the invention was made. As discussed in the rejection, one having ordinary skill in the art would have been motivated to use full length LBLOX or to identify sequences that target LBLOX to lipid bodies, in order to use them to target other proteins, such as enzymes involved in fatty acid/lipid metabolism, to lipid bodies, and make a polynucleotide encoding a fusion comprising said sequence and desaturase, thereby directing the enzyme to the site where its activity is desired

Hence the rejection is maintained.

None of the claims are allowable.

***Conclusion***

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yong Pak whose telephone number is 571-272-0935. The examiner can normally be reached 6:30 A.M. to 5:00 P.M. Monday through Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 571-272-0928. The fax phone numbers for the organization where this application or proceeding is assigned are 571-273-8300 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Yong D. Pak
Patent Examiner 1652

Tekchand Saidha
Primary Patent Examiner 1652